SELECTED PHASE I & II STUDIES

The following is a list of selected phase I studies of new agents available through the CTRC's Institute for Drug Development and the Brooke Army Medical Center (BAMC) that require an ECOG or SWOG performance status of 0-2 and relatively normal hematopoietic (bone marrow), renal, and hepatic function. **There is no specific tumor type required for any of these agents.**

Generally, patients are eligible for a Phase I protocol after they have been treated on a standard treatment regimen, at a time when either their tumor has become larger or it has come back. These patients still have a life expectancy of > 3 months and are still well enough that they are able to take care of themselves most of the time. Patients must also have sufficient bone marrow, kidney, and liver function that they are still candidates for chemotherapy. Patients must have either measurable or evaluable disease by CAT scan or physical exam. Candidates for these protocols can anticipate a 4-week interval between stopping their last therapy and starting treatment on these protocols. Patient referral information is located at the end of this listing or click here. (Rev: 9/2000)

PHASE II OR DISEASE-ORIENTED

LUNG CANCER (NON-SMALL CELL)

CP358,774

CP358,774 is a novel**oral inhibitor of epidermal growth factor receptor (EGF) tyrosine kinase.** This class of agents has demonstrated potent anti-tumor activity in preclinical studies and in preliminary clinical studies. Patients who have stage III and IV disease and have previously demonstrated disease progression or relapse following platinum-containing chemotherapy may be eligible. Initial tumor or biopsy must be demonstrated to be positive for the EGF receptor. Oral compound administered daily.*(Approved at BAMC.)*

HEAD AND NECK CANCER

CP358,774

CP358,774 is a novel **oral inhibitor of epidermal growth factor receptor (EGF) tyrosine kinase** (see LUNG CANCER). Patients with advanced head and neck cancer who may have had up to one prior induction regimen including concomitant chemoradiotherapy or adjuvant chemotherapy. A minimum of six months is required between induction chemotherapy and study treatment. Definitive proof of EGF receptor positive tumor is not required. **Oral** compound administered daily. *(Approved at BAMC.)*

PANCREATIC CANCER

MGI-114

MGI-114 is an active **DNA-targeting agent** that is completely different from any

known agent. This study is evaluating the activity of MGI-114 as a 30-minute infusion daily for 5 days every 4 weeks in advanced or metastatic pancreatic carcinoma following treatment with gemcitabine. Patients MUST have received prior gemcitabine-based therapy. *(Approved at BAMC.)*

DX-8951f (TOPOISOMERASE I INHIBITOR)

A topoisomerase I inhibitor that has completed phase I evaluations. In preclinical studies, the agent is much more potent that either topotecan or irinotecan. Activity has been observed in many tumor types in phase I trials.

This phase II study is evaluating the activity of DX-8951f as a 30-minute infusion daily for 5 days every 3 weeks in patients with advanced and metastatic pancreatic carcinoma. Patients could have received no prior therapy or one chemotherapy regimen. *(Approved at BAMC.)*

SB408075

See "Phase I Immunotherapy/Biologic Therapy/Gene Therapy"

PROSTATE CANCER

DX-8951f (TOPOISOMERASE I INHIBITOR)

A **topoisomerase I inhibitor** that has completed phase I evaluations. In preclinical studies, the agent is much more potent that either topotecan or irinotecan. Activity has been observed in many tumor types in phase I trials, including prostate cancer.

This phase II study is evaluating the activity of DX-8951f as a 30-minute infusion daily for 5 days every 3 weeks in patients with hormone-refractory advanced or metastatic prostate cancer. Patients cannot have received prior cytotoxic chemotherapy. *(Approved at BAMC.)*

G3139 PLUS DOCETAXEL

G3139 and docetaxel are being combined together in a phase I study in patients with hormone-refractory prostate cancer. G3139 is an antisense compound to bcl, which is a cell survival protein. Treatment with G3139 triggers cell death and enhances the effects of docetaxel in preclinical studies. Docetaxel has demonstrated activity in prostate cancer.

LIVER (HEPATOCELLULAR) CANCER

DX-8951f (TOPOISOMERASE I INHIBITOR)

A **topoisomerase I inhibitor** that has completed phase I evaluations. In preclinical studies, the agent is much more potent that either topotecan or irinotecan. Activity has been observed in many tumor types in phase I trials, including liver cancer.

This phase II study is evaluating the activity of DX-8951f as a 30-minute infusion daily for 5 days every 3 weeks in locally advanced or metastatic liver cancer (hepatocellular carcinoma). Patients could have received no prior therapy or one prior chemotherapy regimen. *(Approved at BAMC.)*

COLORECTAL CANCER

ZD1839

A novel **oral inhibitor of epidermal growth factor receptor (EGF) tyrosine kinase** is being combined with a conventional schedule 5-fluorouracil and leucovorin in patients with metastatic colorectal cancer. Patients with advanced colorectal cancer may have received prior treatment with 5-fluororuracil and leucovorin as long as the treatment interval was longer than 6 months. *(Approved at BAMC.)*

SB408075

See "Phase I Immunotherapy/Biologic Therapy/Gene Therapy"

G3139 PLUS IRINOTECAN

G3139 and irinotecan are being combined together in a phase I/II study in patients with metastatic colorectal cancer. G3139 is an antisense compound to bcl, which is a cell survival protein. Treatment with G3139 triggers cell death and enhances the effects of irinotecan in preclinical studies. Irinotecan is an active agent in the treatment of colorectal cancer.

BREAST CANCER

MGI-114

MGI-114 is an active **DNA-targeting agent** that is completely different from any known agent. Major responses have been noted in phase I trials. This study is evaluating the activity of MGI-114 as a 30-minute infusion daily for 5 days every 4 weeks in advanced or metastatic breast cancer who have had no more than 2 prior chemotherapy regimens administered in the metastatic setting (may have had adjuvant chemotherapy). Patients MUST have received prior gemcitabine-based therapy. *(Approved at BAMC.)*

HERCEPTIN + R115,777

See "Phase I: Signal Transduction Inhibitors"

PHASE I: IMMUNOTHERAPY/BIOLOGIC THERAPY/ GENE THERAPY

INTROGEN P53 ADENOVIRUS

Intravenous injection of this attenuated adenovirus that contains the normal tumor suppressor p53 oncogene designed to specifically destroy cells with mutated or abnormal p53. The net effect is to restore p53 suppressor function in tumors. *(Not approved at BAMC.)*

(Consider for all solid tumors, but particularly for head and neck, lung, pancreas, colon, breast, prostate, bladder, and other carcinomas.)

PANOREX + IRINOTECAN (CPT-11)

Panorex is an antibody against an antigen common to adenocarcinomas. It has demonstrated efficacy in European adjuvant trials in patients with colorectal carcinoma. Preclinical studies suggest that the agent is also active against many other tumor types. *(Not approved at BAMC.)*

(Consider for patients with adenocarcinomas, e.g., colon, other GI, breast, and lung.)

SB408075

Humanized monoclonal antibody to the antigen C242 (found on more than 90% of colorectal and pancreatic cancers, as well as other carcinomas). It is attached to the chemotherapeutic agent maytansine. This conjugate has induced prominent activity, including cures, in well-established tumors in preclinical studies. Given once every 3 weeks. *(Approved at BAMC.)*

Consider for all solid tumors, but particularly for colon, pancreas, lung, breast, prostate, bladder, and other carcinomas.)

TAZAROTENE

Novel RAR retinoid with potent anti-tumor properties in a broad spectrum of cancers. Administered as a continuous oral therapy. *(Approved at BAMC.)*

(Consider for all solid tumors.)

PHASE I: SIGNAL TRANSDUCTION INHIBITORS

CP 358,774 AND CI 1033 EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS

Specific **oral** inhibitors of epidermal growth factor receptor (EGF) tyrosine kinase. Oral compounds for chronic, daily treatment. These agents have potent antitumor activities in preclinical studies and in early clinical studies. *(Approved at BAMC.)*

(Consider for all solid tumors, particularly carcinomas.)

CCI-779 ALONE OR WITH GEMCITABINE

CCI-779 is a potent inhibitor of cell signal transduction and an analog of the potent immunomodulatory agent rapamycin. Broad preclinical and clinical activity has been noted in many tumors (e.g., renal, cervix, ovarian) and clinical activity noted in many tumor types to date. A phase I study is evaluating the feasibility of a 1-hour schedule daily for 5 days every 2 weeks. Another study evaluates the combination of CCI-779 and gemcitabine, with both agents administered weekly. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas.)

HERCEPTIN + R115,777

Herceptin is a monoclonal antibody against Her2/neu, which is found in breast cancer and many other types of cancers. It is being administered with R115,777, an oral inhibitor of the signal transduction protein Ras. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas).

PHASE I: OTHER NOVEL AGENTS

FB642

An **oral** agent with **broad preclinical activity** in preclinical studies against refractory human tumors. The agent has a **novel** mechanism of action. It is

administered as a single oral dose weekly x 3 every 4 weeks or daily for 5 consecutive days for 3 weeks every 4 weeks. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas.)

LY231514 (MULTI-TARGETED ANTIFOL)

LY231514 is a multi-targeted antifolate compound and a **thymidylate synthetase inhibitor**. In early studies, the agent has demonstrated consistent activity in patients with colorectal, head and neck, lung, mesothelioma and breast cancers. We are currently evaluating the agent in three separate studies, combined with: 1) folic acid to minimize toxicity; 2) + 5-FU; and 3) + Irinotecan. *(Approved at BAMC.)*

(Consider for all solid tumor s,but particularly for colon, other GI, lung, head and neck, and breast cancers.)

ZD9331 (THYMIDYLATE SYNTHETASE INHIBITOR)

ZD9331 is a **thymidylate synthetase inhibitor** with a relatively long half-life. It is being evaluated as an oral agent and a bolus IV infusion every 3 weeks. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, but particularly colon, other GI, lung, head and neck, and breast cancers.)

DX-8951f (TOPOISOMERASE I INHIBITOR)

A topoisomerase I inhibitor with broad activity in solid tumor studies. It is being evaluated as a 21-day continuous infusion every 4 weeks and as a 30-minute infusion daily for 5 days every 3 weeks. Preliminary clinical antitumor activity observed in several cancers including colon, lung, and hepatoma. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, but particularly for colon, other GI, lung, head and neck, and breast cancers.)

MGI-114 + IRINOTECAN

MGI-114 is an active **DNA-targeting agent** that is completely different from any known agent. Major responses have been noted in phase I trials. This study is evaluating the activity of MGI-114 as a 30-minute infusion daily for 5 days every 4 weeks with irinotecan given on day one. *(Approved at BAMC.)*

(Consider for all solid tumor and lymphomas.)

COL-3

A matrix metalloproteinase inhibitor (angiogenesis inhibitor) administered daily. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas).

9-NITROCAMPTOTHECIN (TOPOISOMERASE I INHIBITOR)

An oral topoisomerase I inhibitor with broad activity against solid tumors. Consistent activity in preliminary clinical studies, particularly against pancreatic carcinoma. It is administered orally for 5 days (Monday through Friday) each week. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, but particularly for colon, other GI, lung, head and neck, and breast cancers.)

PEG-CAMPTOTHECIN

Camptothecin, the prototypic topoisomerase I inhibitor, has been solubilized with polyethylene glycol. PEG-Camptothecin is a pro-drug that releases camptothecin. Potent antitumor properties. Administered as a brief intravenous infusion every three weeks. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, but particularly for colon, other GI, lung, head and neck, and breast cancers.)

NX-211

Liposomal camptothecin derivative with broad activity in phase I/II studies. The liposomal preparation is given weekly x 3 every 4 weeks as a brief infusion. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas.)

BMS-184476 AND RPR116258A (WATER SOLUBLE TAXOL ANALOGS)

Taxane analogs that are much more potent than taxol and taxotere, with potentially broader spectra of antitumor activity against tumors with multidrug resistance. These agents are also more water soluble (requires less or no Cremophor) and can be given as a short injection without premedication. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, including patients who have received previous taxol and taxotere.)

T138067

Novel **antimicrotubule agent targeting the colchicine binding site**. Has a broad sprectrum of anti-tumor activity, active in multi-drug resistant tumors, and penetrates into the CNS. Administered intravenously on two schedules: weekly for 3 weeks every 4 weeks or daily for 5 days every 3 weeks. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, including patients who have received previous taxol and taxotere.)

INTOPLICINE

A potent dual inhibitor of both topoisomerase I and II, it is being administered as a 5-day continuous infusion every 3 weeks using an infusion pump. Central venous access is required. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas.)

TEMOZOLOMIDE

An **oral** alkylating agent with unique clinical activity in patients with melanoma and high grade glioma. The FDA is currently reviewing a new drug application for the use of temozolomide. Recently, broader activity (including in colorectal cancers) has been observed with prolonged oral-dosing schedules. Two studies are evaluating temozolomide: 1) administered daily x 21 days every 4 weeks;

and 2) administered daily x 7 days every other week. *(Approved at BAMC.)*

(Consider for all solid tumors and lymphomas, particularly for patients with melanoma and high grade glioma.)

S1

An **oral fluoropyrimidine** that achieves clinically-relevant 5-FU concentrations. The agent has demonstrated activity against breast and gastrointestinal malignancies. It is administered daily for 4 weeks followed by a 1-week break. Cycles are repeated every 5 weeks. *(Approved at BAMC.)*

(Consider for patients with gastrointestinal and breast cancers).

TROXACITABINE (BCH-4556) AND CISPLATIN OR PACLITAXEL

Troxacitabine (BCH-4556) is a novel nucleoside. Unlike gemcitabine and cytosine arabinoside, it is not rapidly metabolized and, therefore, is retained in the body and tumors. Activity has been reported in many cancers in preclinical and phase I studies. Administered intravenously over 30 minutes in combination with either cisplatin or paclitaxel. *(Approved at BAMC.)*

(Consider for patients with all solid malignancies and lymphoma.)

SR-45023A

Oral agent that targets a novel target in cancer cells called the death receptor, which induces programmed cell death. Administered weekly. *(Approved at BAMC.)*

(Consider for patients with solid malignancies and lymphomas.)

PHASE I: HEPATIC AND RENAL DYSFUNCTION STUDIES

Phase I studies for patients with liver dysfunction (elevations of transaminases and/or bilirubin): currently both **docetaxel (Taxotere)** and **irinotecan (CPT-11)** are being evaluated in patients with hepatic dysfunction, and **LY231514** is being evaluated in patients with renal dysfunction. *(Approved at BAMC.)*

PATIENT REFERRAL

Other studies are also available for the treatment of different kinds of cancer. To refer patients and/or discuss eligibility and other issues related to these or other studies, please contact:

Stephanie Hodges, R.N.
Patient Referral Coordinator
Phase I Department
Grossman Cancer Center
7979 Wurzbach Road
San Antonio, TX 78229
Phone: (210) 616-5798
Fax: (210) 616-5799
E-mail: shodges@saci.org ***(Note: If using e-mail to inquire about clinical trials, please include your phone/fax numbers as additional information is usually needed to provide the best assistance. Thank you!)***

If you wish to view our "What's New!" page for bulletins about new Phase I and II studies recently activated at SACI, please click here.

If you wish to proceed to the Cancer Therapy and Research Center Home Page, click here.

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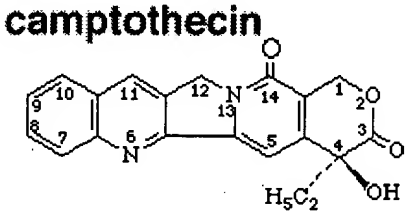
Pharmacology of Camptothecin, Irinotecan and Topotecan

[Chemical Comparison Table | Camptotheca Page]



Camptothecin is a quinoline-based **alkaloid** found in the barks of the Chinese camptotheca tree and the Asian nothapodytes tree. It and its close chemical relatives (aminocamptothecin, **CPT-11 [irinotecan]**, DX-8951f, and **topotecan**) are the only known naturally-occurring DNA topoisomerase I inhibitors. It's one of the newest chemotherapy drugs, and as such cancer researchers are really interested in it, but most incarnations of the drug aren't FDA-approved yet (it and some of its chemical relatives are in clinical trials to treat breast and colon cancers, malignant **melanoma**, small-cell lung cancer, and **leukemia**).

On May 29, 1996, the FDA approved topotecan as a treatment for advanced ovarian cancers that have resisted other chemotherapy drugs. Topotecan, which worked as well as or better than Taxol in clinical trials, is manufactured by SmithKline Beecham Pharmeceuticals and is sold under the trade name Hycamtin.

Also, on June 17, 1996, injectable irinotecan HCl was approved as a treatment for metastatic cancer of the colon or rectum; the drug is available under the generic name irinotecan and will be marketed by Pharmacia & Upjohn under the trade name Camptosar. The drug is normally only prescribed in colorectal cancer cases that haven't responded to standard treatment with the chemotherapy agent fluorouracil.

So what does a DNA topoisomerase I inhibitor do, and how does it fight cancer? Topoisomerases are the **enzymes** that wind and unwind the **DNA** that makes up the **chromosomes**. The chromosomes must be unwound in order for the cell to use the genetic information to synthesize **proteins**; camptothecin keeps the chromosomes wound tight, and so the cell can't make proteins. As a result, the cell stops growing. Because cancer cells grow and reproduce at a much faster rate than normal cells, they are more vulnerable to topoisomerase inhibition than are normal cells.

So far, the major side effects of camptothecin drugs are potentially severe diarrhea, nausea, and lowered **leukocyte** (white blood cell) counts. The drug may also damage bone marrow.

For more information, visit:

- Camptothecins: From Discovery to the Patient
- Ovarian Cancer Research Notebook: Topotecan
- Ovarian Cancer Research Notebook: CPT-11 (Irinotecan)
- Camptosar - Important Facts About Your Chemotherapy
- Topotecan Approved by FDA
- CPT11 and Topotecan
- Q & A on the National Cancer Institute's Natural Products Branch
- Glycosylated Camptothecins

URL: http://biotech.icmb.utexas.edu/botany/cpt.html
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